Journal of Molecular Structure 1157 (2018) 263–275

Contents lists available at ScienceDirect

Journal of Molecular Structure

journal homepage: http://www.elsevier.com/locate/molstruc

Conformational flexibility and packing plausibility of repaglinide polymorphs

Dimpy Rani, Parnika Goyal, Renu Chadha*

University Institute of Pharmaceutical Sciences, Panjab University, Chandigarh, 160014, India

ARTICLE INFO

Article history:
Received 19 August 2017
Received in revised form
6 December 2017
Accepted 11 December 2017
Available online 13 December 2017

Keywords:
Repaglinide
Polymorphs
Crystal structure
Conformational analysis
Crystal packing
Crystal energy landscape

ABSTRACT

The present manuscript highlights the structural insight into the repaglinide polymorphs. The experimental screening for the possible crystal forms were carried out using various solvents, which generated three forms. The crystal structure of Form II and III was determined using PXRD pattern whereas structural analysis of Form I has already been reported. Form I, II and II was found to exist in *P*212121, *PNA*21 and *P*21/*c* space groups respectively. Conformational analysis was performed to account the conformational flexibility of RPG. The obtained conformers were further utilized to obtain the information about the crystal packing pattern of RPG polymorphs by polymorph prediction module. The lattice energy landscape, depicting the relationship between lattice energy and density of the polymorphs has been obtained for various possible polymorphs. The experimentally isolated polymorphs were successfully fitted into lattice energy landscape.

1. Introduction

The conformational flexibility and the crystal packing of the molecules lead to the multiple crystalline forms of a molecule. These various crystal forms *i.e.*, polymorphs have distinguished physicochemical, thermal and spectroscopic properties. For pharmaceuticals, the exploration of the plausible polymorphic form and the stringent control over a therapeutic optimized crystal form is of utmost importance [1,2]. Besides this, in some cases, stable polymorph takes years to nucleate. In this scenario, a demand for an alternative strategy to analyze all the possible polymorphs at low cost and less time arises.

The CSP (Crystal Structure Prediction) has emerged as a useful tool for determining the crystal structure, for accounting the probable conformations and for predicting a range of thermodynamically favored crystal packings [3]. The computational findings along with experimental screening give a way to rational polymorph screening.

In the presented manuscript, the emphasis is laid on the structural aspects of the polymorphic forms of repaglinide (RPG), a poorly water-soluble oral hypoglycemic agent. RPG is a flexible molecule and prone to exhibit the polymorphism. Therefore, different group of workers have tried to explore its polymorphic forms but only three forms could be isolated [4–6]. Out of these, Form I (S-repaglinide) is commercially used in the treatment of diabetes and its crystal structure has been analyzed by Grell *et el.* [4]. However, there is no report available of crystal structure of the other two crystal forms *i.e.*, Form II and Form III. The knowledge of the crystal structure is crucial as the physicochemical properties are dependent on the crystal lattice. This lacuna has been taken into consideration and the presented work illustrates the crystal structure determination of Form II and Form III. Apart from it, RPG molecule has also been subjected to thorough search for probable conformational minimum energy polymorphs (using Polymorph Predictor module in BIOVIA Material Studio) around its rotatable bonds. These were later explored for different crystal packing pattern. The stable conformations of RPG have also been reported by few authors [7–9], but it has not been utilized further to consider the aspect of crystal packing and the paradigm of RPG polymorphs have remained unexplored. In the present work, the synergistic approach of conformational and packing polymorphs has been used to generate a crystal energy landscape, which can be a guide for further mapping of potential polymorphs of RPG.

* Corresponding author. Pharmaceutical Chemistry, University Institute of Pharmaceutical Sciences, Panjab University, Chandigarh, 160014, India.
E-mail address: renukchadha@rediffmail.com (R. Chadha).

https://doi.org/10.1016/j.molstruc.2017.12.036
0022-2860/

2. Experimental

2.1. Materials

RPG (≥99%, Form I) was obtained from Terrace Pharmaceutical Pvt Ltd, Mohali, India, as a gift sample. All the chemicals and solvents were purchased from Sigma-Aldrich or E. Merck Ltd, and used as received.

2.2. Preparation of polymorphic forms

Form I was procured as commercial sample and subjected to crystallization in various solvents and mixture of solvents. The list of solvents includes dimethylformamide, methyl acetate, propyl acetate, n-butyl acetate, xylene, acetylacetone, dichloromethane and 1,2-dichloroethane. The crystals of white color were obtained from dimethylformamide, methyl acetate, propyl acetate and n-butyl acetate whereas a white solid mass was collected from xylene, acetylacetone, dichloromethane and 1,2-dichloroethane. The crystals were dried at room temperature and solid mass was dried at a temperature of 40 °C. After drying, the products were characterized using various analytical techniques.

2.3. Characterization

The crystallized products were characterized by Differential Scanning Calorimetry (DSC) and Powder X-ray Diffraction (PXRD).

DSC thermograms were obtained under nitrogen atmosphere (flow rate 50 ml/min), using Q 20 (TA-Instruments Inc., USA) model. The samples were sealed in aluminium pans and heated in the range of 25–250 °C, at ramp rate of 10 °C/min. PXRD were obtained by PANalytical X'Pert Pro X-ray powder diffractometer (The Netherlands, Holland) with Cu source, in the range of 5°–45° (2θ).

2.4. Crystal structure determination from PXRD

The crystal structure of different identified crystal forms were done by Material studio (BIOVIA 7.0) software. The PXRD was indexed for obtaining the unit cell using X-CELL method. The generated unit cell was subjected to pawley refinement and further to space group search. The geometrically optimized structure of RPG with the consideration of torsional flexibility was placed in unit cell and powder solve was done. The obtained crystal structure was further refined by reitveld refinement to get best possible crystal structure.

2.5. Conformational searches

RPG molecule was sketched and optimized geometrically by smart algorithm in Forcite module using COMPASS forcefield. Later the conformational sampling of RPG was executed by conformer module of BIOVIA material studio. The systematic grid conformational search with geometry optimization and restraints method was done by varying one out of 11 torsion angles. The restraint force constant was kept at 1000 kcal/mol/rad$^{\Lambda}$2. The torsions were varied from −180° to 180°, in 120 steps with 1.3° of interval. The search of geometrically optimized conformer with low energy was performed by atom based summation method using pcff forcefield. The perturbation in the energy of conformers with the change in torsion angles was studied. The lowest energy conformers were re-optimized for energy by Dmol^3 using gradient-corrected generalized gradient approximations (GGA) and PBE functional in density functional theory (DFT) calculations with double numeric plus polarization (DNP) basis set. The electrostatic potential (ESP) charge was generated on the re-optimized conformer.

2.6. Global search

The identified stable conformers in the conformational search were subjected for search of global minima. The polymorph predictor module of BIOVIA material studio was used to estimate the crystal packing of different chosen conformers in most common space groups (*P*21/C, *P*1, *P*212121, *P*21, C2/C, *PBCA*, *PNA*21, *PBCN*, *CC*, and *C*2). The prediction was performed by Ewald summation for electrostatic interactions and by atom based summation for the Van der Waals forces using COMPASS forcefields. The polymorph prediction job serves the energy optimized, potential crystal packing of various conformers in different space groups. The clustering was performed after both packing search and energy optimization step, to remove the duplicate entries. The crystal energy landscape (energy vs density graph) for all the potential polymorphs was plotted to gain an insight into the paradigm of RPG polymorphs.

3. Results and discussion

3.1. Characterization of crystallized polymorphs

In the preliminary step of characterization, the obtained crystallized products (crystallization of Form I of RPG) from the various solvents were subjected to DSC (Fig. 1). The crystals from dimethylformamide, methyl acetate, propyl acetate and n-butyl acetate show sharp melting endotherm at 134.11 °C, 134.88 °C, 134.46 °C and 135.04 °C respectively. The melting endotherm of these forms is in the range, reported for Form I of RPG. The re-crystallized product from xylene, acetylacetone, dichloromethane and 1,2-dichloroethane shows melting endotherm at 100.14 °C, 98.16 °C, 76.49 °C and 77.41 °C respectively. The comparison of melting point of crystalline solids from xylene and acetylacetone, with the literature suggested them to be Form II. Besides this, the melting behavior of the crystalline solids collected from dichloromethane and 1,2-dichloroethane resembles the Form III. The isolated crystalline forms resembled the reported forms as far as DSC and PXRD data (Fig. 2) is concerned but no report is available regarding their three dimensional structures. To gain the insight into the structural parameters, the detailed crystal structure was determined using PXRD data.

3.2. Crystal structure determination from PXRD

The crystal structure of Form I of RPG is determined by Grell *et el.* but the supramolecular architecture has not been described in detail (4). In the present work, an attempt was done to elaborate the packing pattern of molecules in the crystal lattice. The Form I crystallize in orthorhombic crystal system with $P2_12_12_1$ space group (ORTEP diagram, Fig. 3(a)). One molecule of RPG is connected to two other adjacent molecules of RPG. The −NH of amide group of RPG interacts with carbonyl oxygen of carboxylic group (N2—H35···O3) of another RPG molecule whereas carbonyl oxygen of amide group forms hydrogen bond with carboxylic −OH (O4—H36···O1) of different RPG molecule (Fig. 3(b)). The molecules are packed in two different types of layers, inclined at an angle of 40.31° to each other. The molecules in the same plane are attached through N—H···O while O—H···O hydrogen bond joins the layers in different planes (Fig. 3(c)).

Form II of RPG crystallizes in orthorhombic crystal system with PNA21 space group (ORTEP diagram, Fig. 4(a)). In the crystal lattice of this crystal form, the −NH of amide group of one molecule forms hydrogen bond with carbonyl oxygen of carboxylic group (N2—H35···O3) of another molecule (Fig. 4(b)). The molecules are arranged in an infinite wavy chained pattern in which one molecule of RPG is attached to adjacent bonded RPG molecules by an angle of